BRCA Timeline: DoD Breast Cancer Research Program (BCRP) and Ovarian Cancer Research Program (OCRP) Research Contributions

BRCA gene mutations have been linked to increased breast and/or ovarian cancer risk. The Department of Defense (DoD) Breast Cancer Research Program (BCRP) and Ovarian Cancer Research Program (OCRP) play a leading role in the fight against these diseases. This interactive timeline shows both milestones in the field and research efforts funded by the DoD.

Year	Title	BRCA Milestones and DoD BCRP/OCRP Research Contributions	Additional Information and Hyperlinks
1990	BRCA1 was Identified	**MILESTONE FROM THE FIELD:** Mary-Claire King names BRCA1 after linking the gene to chromosome 17 using a large group of families with cases of early-onset breast cancer.	• Hall J, Lee M, Newman B, et al. 1990. Linkage of early-onset familial breast cancer to chromosome 17q21. Science 250(4988):1684-1689.
1993	Risks Identified (Risk)	Under a BCRP Investigator-Initiated Award, Dr. David Goldgar, Dr. Susan Neuhausen, and colleagues at the University of Utah were part of the team that isolated, cloned, and performed the initial characterizations of the BRCA2 gene. Successful cloning of the gene allowed these investigators to analyze BRCA2 mutations in high-risk individuals and their relatives in order to ascertain their cancer risks. Using PCR-based techniques, this research team was the first to positively identify the founder BRCA2 617delT mutation in Ashkenazi Jewish women and identified the founder BRCA2 999del5 mutation in Icelanders.	• BCRP Abstract • Wooster R, Bignell G, Lancaster J, et al. 1995. Identification of the breast cancer susceptibility gene BRCA2. Nature 378:789-792. • Neuhausen S, Gilewski T, Norton L, et al. 1996. Recurrent BRCA2 6174delT mutations in Ashkenazi Jewish women affected by breast cancer. Nat Genet 13:126-128. • Thorlacius S, Olafsdottir G, Tryggvadottir L, et al. 1996. A single BRCA2 mutation in male and female breast cancer families from Iceland with varied cancer phenotypes. Nat Genet 13:117-119.
1993	Established Regional Centers (Risk)	The 1993 BCRP granted Dr. Mary Daly at Fox Chase Cancer Center a Tumor Sample, Breast Tissue, and Cell Line Repository Award, which aided in the development and expansion of one of the first regional centers for cancer risk, with a focus on breast cancer. The lessons learned in developing this infrastructure helped other institutions set up similar centers. The OCRP then gave Dr. Paul Engstrom a Program Project Award in 1997 to expand this infrastructure to include families with a history of ovarian cancer in an effort to explore risk for this disease. The center evolved into a program that serves Philadelphia and surrounding communities with a range of risk assessment, screening, and preventive services.	• BCRP Abstract for Dr. Mary Daly • OCRP Abstract for Dr. Paul Engstrom • Fox Chase Cancer Center's Risk Assessment Program
1993	Gene Mapping Strides (Screening)	Under a BCRP Investigator-Initiated Award, Dr. Steven Narod at the Montreal General Hospital Research Institute made important contributions to the genetic analysis of BRCA1, specifically in mapping the location of the gene within the chromosome. By sharing his genetic recombination discoveries with collaborators, the BRCA1 gene was assigned a genetic interval of 600kb. Dr. Narod made use of his extensive collection of clinical samples and contributed to discovery of recurrent mutations in Canadian families, enabling penetrance analysis of breast and ovarian cancer in carriers of BRCA mutations. Today, his database of nearly 13,000 women from 30 countries supports numerous international collaborations.	• BCRP Abstract • Rommens J, Durocher F, McArthur J, et al. 1995. Generation of a transcription map at the HSD17B locus centromeric to BRCA1 at 17q21. Genomics 28(3):530-542. • Phelan C, Rebbeck T, Weber B, et al. 1996. Ovarian cancer risk in BRCA1 carriers is modified by the HRAS1 variable number of tandem repeat (VNTR) locus. Nat Genet 12(3):309-311. • Narod S, Risch H, Moslehi R, et al. 1998. Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. N Engl J Med 339(7):424-428.

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1993	Complexities of Genetic Testing (Screening)	With the discovery of BRCA gene mutations, the cancer risk of a patient who carries a BRCA1 or BRCA2 germ-line mutation could be determined with a high degree of accuracy. Under a BCRP Investigator-Initiated Award, Dr. Henry Lynch of Georgetown University conducted the largest assessment and monitoring project of its kind to avoid or minimize adverse psychological consequences to patients undergoing genetic testing for BRCA mutations. Dr. Lynch used linkage analysis to identify high-risk individuals and provided genetic counseling and Family Information Sessions to these individuals and their relatives. This study found that genetic testing for BRCA mutations is highest among persons who have multiple relatives affected with cancer, suggesting that cancer-specific distress motivates BRCA testing. Rates of depression were found to be significantly higher among subjects who declined genetic testing. These findings contributed to a change in clinical practice, alerting physicians to the benefits and complexities of genetic susceptibility testing.	• BCRP Abstract • Lerman C, Hughes C, Lemon S, et al. 1998. What you don't know can hurt you: Adverse psychologic effects in members of BRCA1-linked and BRCA2-linked families who decline genetic testing. J Clin Oncol 16(5):1650-4. • Lerman C, Narod S, Schulman K, et al. 1996. BRCA1 testing in families with hereditary breast-ovarian cancer. A prospective study of patient decision making and outcomes. JAMA 275:1885-92.
1994	BRCA1 Cloned	**MILESTONE FROM THE FIELD:** Mark Skolnick and colleagues at Myraid Genetics announced they have cloned the BRCA1 gene. The identification of truncating mutations in the coding sequence of BRCA1 in families with multiple cases of breast cancer was the conclusive step.	• Miki Y, Swensen J, Shattuck-Eidens D, et al. 1994. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 266(5182):66-71.
1994	BRCA2 Link	**MILESTONE FROM THE FIELD:** BRCA2 was linked to chromosome 13 by Wooster et al.	• Wooster R, Neuhausen S, Mangion J, et al. 1994. Localization of breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. Science 265(5181):2088-90.
1994	BRCA1 Mutations Linked to Jewish Ancestry	**MILESTONE FROM THE FIELD:** In the years immediately after the identification of *BRCA1*, several research teams undertook the categorization of mutations in different populations. In the first wave of findings, Dr. Jacques Simard and colleagues identified recurrent mutations in a small series of families from Quebec, Canada. Two mutations were seen more than once (185delAG and 5382insC), and families with these mutations were found to be of Jewish ancestry. Two years later, Dr. Kenneth Offit and Dr. Susan Neuhausen identified a third mutation (*BRCA2* 6174delT) also associated with Jewish ancestry.	• Simard J, Tonin P, Durocher F, et al. 1994. Common origins of BRCA1 mutations in Canadian breast and ovarian cancer families. Nat Genet 8:392-398. • Neuhausen S, Gilewski T, Norton L, et al. 1996. Recurrent BRCA2 6174delT mutations in Ashkenazi Jewish women affected by breast cancer. Nat Genet 13:126-128.
1995	BRCA2 Cloned	**MILESTONE FROM THE FIELD:** BRCA2 was cloned by Wooster et al.	• Wooster R, Bignell G, Lancaster J, et al. 1995. Identification of the breast cancer susceptibility gene BRCA2. Nature 378(6559):789-792.
1995	In Vitro Translation Technique Adopted	**MILESTONE FROM THE FIELD:** The research community adopted the *in vitro* translation technique, also known as the protein-truncation test (PTT), to screen for BRCA mutations.	• Hogervorst F, Cornelis R, Bout M, et al. 1995. Rapid detection of BRCA1 mutations by the protein truncation test. Nat Genet 10(2):208-212.

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1995	BRCA1/2 Linked to Ovarian Cancer Risk	**MILESTONE FROM THE FIELD:** BRCA1/2 gene mutations linked to increased ovarian cancer risk.	
1995	Male Breast Cancer and BRCA2 (Risk)	Under a BCRP New Investigator Award, Dr. Susan Neuhausen, of the University of Utah and in collaboration with Dr. David Goldgar, collected the largest single-site set of male breast cancer cases and estimated the risk due to BRCA2 mutations. Dr. Neuhausen concluded that family history is not a good predictor of BRCA2 status; however, family history was found to be associated with an earlier age at diagnosis of male breast cancer in general. In addition, when male breast cases were selected based on the presence of other mutations, including the founder 6174delT mutation, mutations in the BRCA2 gene were found to be more prevalent in the unselected cases. This suggested the presence of novel variants associated with male breast cancer. Several years later, Dr. Neuhausen used the samples collected under her BCRP award to perform a genome-wide association study of male breast cancer. A common variant in the gene RAD51B was found to be associated with male breast cancer risk, and a landmark paper was published describing this finding.	• BCRP Abstract • Orr N, Lemnrau A, Cooke R, et al. 2012. Genome-wide association study identifies a novel variant in RAD51B associated with male breast cancer risk. Nat Genet 44(11):1182-1184.
1995	Breast Cancer Risk and TP53 Mutations (Risk)	Under a BCRP Investigator-Initiated Award, Dr. Jorunn Eyfjord of the Icelandic Cancer Society was the first to assess the relationship between risk factors for breast cancer and the occurrence of TP53 mutations. Dr. Eyfjord confirmed that TP53 mutations in Icelandic women diagnosed with breast cancer are markedly different in BRCA2 mutation carriers as compared with non-carriers. Today, TP53 mutations are considered a hallmark of "BRCAness" or the degree with which sporadic cancers share traits with those occurring in BRCA mutation carriers.	• BCRP Abstract • Thorlacius S, Olafsdottir G, Tryggvadottir L, et al. 1996. A single BRCA2 mutation in male and female breast cancer families from Iceland with varied cancer phenotypes (see comments). Nat Genet 13(1):117-119. • Gretarsdottir S, Thorlacius S, Valgardsdottir R, et al. 1998. BRCA2 and p53 mutations in primary breast cancer in relation to genetic instability. Cancer Res 58(5):859-862.
1995	BRCA1/2 and DNA Repair (Screening)	At the time Dr. Gail Tomlinson received a BCRP New Investigator Award, BRCA1 and BRCA2 were associated with breast cancer risk, but their function in the cell was still unknown. Dr. Tomlinson and her team at the University of Texas Southwestern Medical Center at Dallas developed experimental tools to determine how BRCA1 and BRCA2 mutations affected DNA double-stranded break repair, including a tumor cell line derived from a 24-year-old patient with a germ-line BRCA1 mutation. She showed definitively that BRCA1 and BRCA2 have a critical function in DNA recombination and repair.	• BCRP Abstract • Tomlinson E, Chen T, Stastny V, et al. 1998. Characterization of a breast cancer cell line derived from a germ-line BRCA1 mutation carrier. Cancer Res 58:3237-3242.
1996	BRACAnalysis Introduced	**MILESTONE FROM THE FIELD:** Myriad introduced the first molecular diagnostic test, BRACAnalysis®, which has become the standard of care.	• Brief History of Myriad

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1996	ATM Deficiency and Breast Cancer (Risk)	Under a BCRP Postdoctoral Fellowship, Drs. Nicholas Ting and Lei Zheng, mentored by Dr. Wen-Hwa Lee at the University of Texas Health Science Center at San Antonio, provided the first evidence of a functional connection between ATM, the gene mutated in ataxia telangiectasia, and BRCA1 in cellular response to DNA damage. This group discovered a novel DNA damage response pathway involving both BRCA1 and ATM, a finding that enabled the now widely accepted link between ATM deficiency and breast cancer.	• BCRP Abstract • Li S, Ting N, Zheng L, et al. 2000. Functional link of BRCA1 and ataxia telangiectasia gene product in DNA damage response. Nature 406:210-215.
1997	Outcomes for BRCA1 Mutation Carriers (Risk)	Dr. William Foulkes at McGill University, with funding from a BCRP Idea Award, assessed the ability of BRCA1 mutations to predict survival among a retrospective cohort of Ashkenazi Jewish women with breast cancer. He demonstrated that BRCA1 mutation was an independent prognostic indicator for overall survival, and he found evidence that overall survival of BRCA1 mutation carriers was reduced if they did not receive adjuvant chemotherapy or hormonal therapy. This work was among the first published reports that BRCA1 mutations were an adverse prognostic factor in a sub-population of breast cancer cases.	• BCRP Abstract • Chappuis P, Rosenblatt J, and Foulkes W. 1999. The influence of familial and hereditary factors on the prognosis of breast cancer. Ann Oncol 10(10):1163-1170. • Chappuis P, Kapusta L, Begin L, et al. 2000. Germline BRCA1/2 mutations and p27(Kip1) protein levels independently predict outcome after breast cancer. J Clin Oncol 18(24):4045-4052.
1997	BRCA1/BRCA2 Role Characterized (Prevention)	Supported by a BCRP Idea Award, Dr. Maria Jasin, from Memorial Sloan-Kettering Cancer Center, developed a way to characterize the role of BRCA1 and BRCA2 in intra-chromosomal double-strand break repair – her cellular system produced a functional fluorescent protein only through successful DNA repair. With this tool, Dr. Jasin showed that cells deficient in these genes were defective in homology-directed chromosomal break repair. Correcting one of the two mutated chromosomal BRCA1 alleles restored chromosome stability. This work further solidified the important roles of BRCA1 and BRCA2 in chromosomal DNA repair. Control and analysis of this repair pathway was subsequently examined for preventative measures that could eliminate BRCA-deficient cells before they arise and therefore decrease the propensity to develop breast cancer.	• BCRP Abstract • Moynahan M, Cui T, and Jasin M. 2001. Homology-directed DNA repair, mitomycin-c resistance, and chromosome stability is restored with correction of BRCA1 mutation. Cancer Res 61:4842. • Moynahan M, Pierce A, and Jasin M. 2001. BRCA2 is required for homology-directed repair of chromosomal breaks. Mol Cell 7(2):263-272.
1998	Prophylactic Surgery Concept	**MILESTONE FROM THE FIELD:** Prophylactic surgery thought to help prevent breast and ovarian cancer in women at high risk.	

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1999	Environmental Impact on BRCA1 (Risk)	Only a small fraction of ovarian and breast cancers are caused by mutations in the BRCA1 gene, indicating other mechanisms contribute to BRCA1-mediated oncogenesis. Supported by a BCRP Idea Award, Dr. Donato Romagnolo from the University of Arizona, Tucson explored the possibility that polycyclic aromatic hydrocarbons (PAHs) – carcinogens present in pollutants such as tobacco smoke, industrial waste, and vehicle exhaust – contribute to ovarian and breast cancer by disrupting BRCA1 expression. He found that PAHs lowered BRCA1 expression in breast cancer cells by inhibiting the BRCA1 promoter and consequently BRCA1 mRNA transcription. These findings characterize a molecular mechanism by which environmental pollutants can disrupt BRCA1 expression and increase the risk for ovarian and breast cancer.	• BCRP Abstract • Jeffy B, Chirnomas R, and Chen E. 2002. Activation of the aromatic hydrocarbon receptor pathway is not sufficient for transcriptional repression of BRCA-1: Requirements for metabolism of benzo[a]pyrene to 7r,8t-dihydroxy-9t,10-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene. Cancer Res 62:113-121.
1999	Quality of Life After Oophorectomy (Prevention)	Dr. Mary Daly received an OCRP Idea Award to evaluate quality of life after prophylactic oophorectomy in women with an increased risk of ovarian cancer, including those with BRCA mutations. This led to the production of her book to aid in decision-making regarding preventive surgery entitled “Ovarian Cancer Risk-Reducing Surgery: A Decision-Making Resource," which is available at no cost online or in print free of charge from the Fox Chase Center (send an e-mail to surgerybook@fccc.edu).	• OCRP Abstract • OCRP Research Highlight • OCRP Video Vignette
1999	Effect of BRCA2 on Protein Function (Treatment)	Under a BCRP Idea Award, Dr. Fergus Couch of the Mayo Clinic and Foundation established a set of functional assays to characterize the effect of BRCA2 mutations on protein function. Using a combination of these assays and bioinformatic modeling, Dr. Couch established that the D2723H mutation is deleterious to BRCA2 function. The findings characterized the mechanism by which D2723H disrupts BRCA2 function, which could lead to the development of improved treatment strategies for individuals with D2723H as well as other BRCA2 mutations.	• BCRP Abstract • Wu K, Hinson S, Ohashi A, et al. 2005. Functional evaluation and cancer risk assessment for BRCA2 unclassified variants. Cancer Res 65(2):417-426.
2000	53BP1's Role in Regulating BRCA1 (Prevention)	BRCA1' s ability to repair DNA in response to damage is enabled by an elaborate surveillance mechanism, called a DNA damage checkpoint, by which BRCA1 is phosphorylated following DNA double-strand breaks. Under a BCRP Idea Award, Dr. Stephen Elledge discovered that 53BP1 is a binding partner of BRCA1 and a crucial part of this signaling network. Following DNA damage, 53BP1 phosphorylates BRCA1, and their interaction is abolished, freeing BRCA1 to translocate within the nucleus and perform DNA repair. The full extent of 53BP1's role in regulating BRCA1 and its DNA repair activities continues to be an active area of research.	• BCRP Abstract • BCRP Video Vignette • BCRP Video Transcript • Era of Hope Plenary Presentation Video • Wang B, Matsuoka S, Carpenter P, et al. 2002. 53BP1, a mediator of the DNA damage checkpoint. Science 298(5597):1435-1438. • Lin S, Li K, Steward G, et al. 2004. Human Claspin works with BRCA1 to both positively and negatively regulate cell proliferation. Proc Natl Acad Sci USA 101(17):6484-6489.

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2000	Prospective Ovarian Cancer Data Bank (Screening)	Dr. David Bowtell used his Program Project Award from OCRP to collect a huge number of well-annotated samples that allow for exploration of genetic and lifestyle risk, and the identification of beneficial treatments depending on genotype (Australian Ovarian Cancer Study). Today, other investigators may apply to use this dataset for their research.	• OCRP Abstract • OCRP Research Highlight • OCRP Video Vignette • OCRP Video Vignette Transcript • Kelemen L, Spurdle A, Purdie D, et al. 2005. RAD52 Y415X truncation polymorphism and epithelial ovarian cancer risk in Australian women. Cancer Lett 218(2):191-197. • Goode E, Chenevix-Trench G, Song H, et al. 2010. A genome-wide association study identifies susceptibility loci for ovarian cancer at 2q31 and 8q24. Nat Genet 42(10):874-879. • Pharoah P, Tsai Y, Ramus S, et al. 2013. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. Nat Genet 45(4):362-370.
2000	Contralateral Risk Findings (Treatment)	Supported by a BCRP Idea Award, Dr. Mark Robson conducted a long-term study to assess the impact of radiotherapy, adjuvant chemotherapy, and breast-conserving therapy on breast cancer risk in a population of Ashkenazi women, a population in which an appreciable number of breast cancers are BRCA-related. The study found that women with BRCA-associated breast carcinoma who undergo breast-conserving surgery and/or radiation therapy do not have an increased risk for true recurrence in the same breast; however, they may have an increased risk of a second primary malignancy within the treated breast. When investigating risk of primary breast cancer in the untreated (contralateral) breast, it was found that women with BRCA1/BRCA2 mutations have a substantially increased risk. Dr. Robson concluded that increased contralateral risk may be attributed to occult lesions existing in the untreated breast that proceed unimpeded in their progression to malignancy. Preliminary data from this study suggested that tamoxifen use was associated with a lower risk of contralateral breast cancer. Taken together, these findings suggest that several factors should be considered when treating BRCA1/BRCA2-associated breast cancer, including appropriate breast surgical options and tamoxifen treatment.	• BCRP Abstract • Robson M, Chappuis P, Satagopan J, et al. 2004. A combined analysis of outcome following breast cancer: Differences in survival based on BRCA1/BRCA2 mutation status and administration of adjuvant treatment. Breast Cancer Res 6(1):R8-R17.

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2001	Understanding Molecular Mechanisms (Risk)	With support from BCRP research and training awards, Dr. Junjie Chen and his research team made significant contributions to the field of DNA damage responsive pathways and BRCA binding proteins. Under a Career Development Award to the Mayo Clinic, followed by an Era of Hope Scholar Award to the University of Texas MD Anderson Cancer Center, Dr. Chen identified and characterized several components, such as the BRCA1-associated protein RAP80, critical for the recruitment of BRCA1 to DNA damage sites. Dr. Irene Ward, a postdoctoral fellow in Dr. Chen's lab at the Mayo Clinic, uncovered the first evidence that the protein 53BP1 participates with BRCA1 and p53 in the DNA damage response, an important biological role of 53BP1 in tumor suppression. These investigations by Dr. Chen and his research group have led to a better understanding of the molecular mechanisms underlying genomic instability and BRCA-associated tumorigenesis.	• BCRP Career Development Award Abstract – Dr. Junjie Chen • BCRP Era of Hope Scholar Award Abstract – Dr. Junjie Chen • BCRP Postdoctoral Traineeship Award Abstract – Dr. Irene Ward • Kim H, Chen J, and Yu X. 2007. Ubiquitin-binding protein RAP80 mediates BRCA1-dependent DNA damage response. Science 316(5828):1202-1205. • Huang J and Chen J. 2008. VprBP targets merlin to the Roc1-Cul4A-DDB1 E3 ligase complex for degradation. Oncogene 27(29):4056-4064. • Sy S, Huen M, and Chen J. 2009. PALB2 is an integral component of the BRCA complex required for homologous recombination repair. Proc Natl Acad Sci USA 106(17):7155-7160. • Feng L, Fong K, Wang J, et al. 2013. RIF1 counteracts BRCA1-mediated end resection during DNA repair. J Biol Chem 288(16):11135-11143.
2001	Ovarian Cancer Association Consortium (Prevention)	Supported by an OCRP Program Project Award, Dr. Andrew Berchuck at Duke University Medical Center formed the international Ovarian Cancer Association Consortium (OCAC) in 2005. The group includes over 50 case-control studies and is working together to identify ovarian cancer susceptibility polymorphisms and lifestyle risks for ovarian cancer. Advancements include the finding that tubal ligation significantly reduced risk for invasive endometrioid and clear cell ovarian cancer, with lesser reduction in risk seen for invasive serous and mucinous ovarian cancers.	• OCRP Abstract • OCRP Research Highlight, 2003 • OCRP Research Highlight, 2009 • Sieh W, Salvador S, McGuire V, et al. 2013. Tubal ligation and risk of ovarian cancer subtypes: A pooled analysis of case-control studies. Int J Epidemiol 42(2):579-589.
2002	BRCA2 Link to Fanconi Anemia	**MILESTONE FROM THE FIELD:** A rare form of Fanconi anemia was shown to be caused by biallelic mutations in *BRCA2.*	• Howlett N, Taniguchi T, Olson S, et al. 2002. Biallelic inactivation of BRCA2 in Fanconi anemia. Science 297(5581):606-609.
2002	Oophorectomy Confirmed as Protective (Prevention)	Through support from a BCRP Physician-Scientist Training Award, Dr. Noah Kauff, under mentorship of Dr. Kenneth Offit of Memorial Sloan-Kettering Cancer Center, was the first to corroborate risk-reducing salpingo-oophorectomy (RRSO) recommendations specifically with BRCA carriers. Until this group's work, only retrospective studies, where participants were not previously genotyped prior to preventive surgery, had been conducted. The results from this study confirmed that RRSO is profoundly protective against subsequent breast and gynecologic cancers in carriers of mutations in BRCA1 and BRCA2. The results also suggested that the magnitude of protection against subsequent breast cancer differed between carriers of BRCA1 and BRCA2 mutations. These important conclusions enabled this preventive surgical procedure to become appropriately integrated into the routine management of women with BRCA mutations.	• BCRP Abstract • Kauff N, Domchek S, Friebel T, et al. 2008. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: A multicenter, prospective study. J Clin Oncol 26(8):1331-1337.

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2003	BRCA2 Linked to Childhood Disease	**MILESTONE FROM THE FIELD:** Children with medulloblastoma or Wilms' tumour were shown to carry two truncating *BRCA2* mutations.	• Offit K, Levran O, Mullaney B, et al. 2003. Shared genetic susceptibility to breast cancer, brain tumors, and Fanconi anemia. J Natl Cancer Inst 95(20):1548-1551.
2003	Gene Inactivation and Ovarian Cancer (Risk)	The majority of inherited cases of epithelial ovarian cancer result from mutation in the BRCA1 gene, which is often accompanied by mutations in the tumor suppressor gene p53. Dr. Denise Connolly at Fox Chase Cancer Center, using funding from an OCRP New Investigator Award, sought to evaluate the effects of inactivating the BRCA1 and p53 genes ovarian epithelial cells in mice. Surprisingly, only about half of the mice with gene inactivation developed tumors, and these tumors shared histologic characteristics with high-grade leiomyosarcomas, which account for approximately 3% of human ovarian tumors. Findings from the study of this model of ovarian leiomyosarcomas may be applied to the understanding of other types of ovarian cancer and sarcomas.	• OCRP Abstract • OCRP Research Highlight • OCRP Video Vignette • OCRP Video Vignette Transcript • Quinn B, Brake T, Hua X, et al. 2009. Induction of ovarian leiomyosarcomas in mice by conditional inactivation of BRCA1 and p53. PLoS One 4(12):e8404.
2003	Improved Risk Assessment (Risk)	Under a BCRP Idea Award, Dr. Fergus Couch of the Mayo Clinic conducted a genome-wide association study (GWAS) involving 11,000 BRCA1 mutation carriers to identify risk modifiers for breast cancer. Furthermore, under an OCRP Idea Development Award, Dr. Couch expanded the GWAS to validate candidate ovarian cancer risk modifiers for BRCA1 mutation carriers. To date, he has successfully identified a novel BRCA1 carrier breast cancer risk modifier locus on chromosome 1q32 and two novel ovarian cancer risk modifier loci for BRCA1 mutation carriers on chromosomes 4q32 and 17q21.	• BCRP Abstract

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2004	PALB2 Discovery (Risk)	With support from a BCRP Postdoctoral Traineeship, and under the mentorship of Dr. David Livingston, Dr. Bing Xia set out to discover new components of BRCA-containing protein complexes and identified a novel protein, Partner and Localizer of BRCA2 (PALB2), as a major physiological nuclear partner of BRCA2. Dr. Xia found that PALB2 co-localizes with BRCA2 in the cell nucleus, promoting stability and enabling DNA repair and checkpoint functions. Dr. Xia further established that mutations in BRCA2 disrupted PALB2 binding and disabled tumor suppressor function. A year after Dr. Xia's discovery of the protein, clinical investigations demonstrated that mutations in the PALB2 gene conferred a 2.3-fold higher risk of breast cancer in individuals with a strong family history and PALB2 was officially coined a breast cancer susceptibility gene. Because the Fanconi anemia and BRCA networks are considered interconnected, it subsequently became clear that mutations in PALB2 also predispose to childhood cancer. Recently, PALB2 has further been identified as a susceptibility gene for familial pancreatic cancer. Dr. Xia's discovery of PALB2 was the first report of this BRCA2 binding protein, and the subsequent identification of PALB2 as a cancer predisposition gene has enabled a clearer picture of the genetic architecture of cancer susceptibility.	• BCRP Abstract • Xia B, Sheng Q, Nakanishi K, et al. 2006. Control of BRCA2 cellular and clinical functions by a nuclear partner, PALB2. Mol Cell 22:719-729.
2004	MLPA Analysis Becomes Standard (Risk)	Under a BCRP Era of Hope Scholar Award, Dr. Nazneen Rahman of the Institute for Cancer Research, London, evaluated the contribution of different types of BRCA1 and BRCA2 gene mutations to breast cancer susceptibility using a simple, cost-effective copy number analysis technique, called multiplex ligation-dependent probe amplification (MLPA). At the time of this award, BRCA gene mutations, such as deletions and duplications, were not detectable by standard PCR-based amplification methods because the deletion or duplication in the BRCA gene sequence was often in low copy number and therefore not amplified. Analyses under this award resulted in the identification of genomic duplication/deletion abnormalities in 4% of BRCA-mutated breast cancers, and demonstrated that MLPA should be undertaken as part of the genetic testing for familial breast cancers. Consequently, MLPA analysis in combination with gene sequencing is now a standard for genetic testing in clinical diagnostic laboratories throughout the United Kingdom and most of Europe. In addition to these advances, Dr. Rahman made substantial contributions to delineating the genetic landscape of breast cancer into three strata: rare, high penetrance genes; rare, intermediate-penetrance genes; and common, low-penetrance genes.	• BCRP Abstract • BCRP Research Highlight • Seal S, Thompson D, Renwick A, et al. 2006. Truncating mutations in the Fanconi anemia J gene BRIP1 are low-penetrance breast cancer susceptibility alleles. Nat Genet 38(11):1239-1241. • Renwick A, Thompson D, Seal S, et al. 2006. ATM mutations that cause ataxia-telangiectasia are breast cancer susceptibility alleles. Nat Genet 38(8):873-875. • Rahman N, Seal S, Thompson D, et al. 2007. PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. Nat Genet 39(2):165-167.

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2005	PARP Enzymatic Activity	**MILESTONE FROM THE FIELD:** BRCA1 or BRCA2 dysfunction unexpectedly and profoundly sensitizes cells to the inhibition of poly(ADP-ribose) polymerase (PARP) enzymatic activity.	• Farmer H, McCabe N, Lord C, et al. 2005. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 434(7035):917-921.
2006	BRCA Mutation Carrier Specimen Repository (Screening)	Under an OCRP Idea Development Award, Dr. Patricia Shaw at University Health Network, Toronto, established a repository of prophylactic surgery specimens from BRCA mutation carriers and investigated putative serous cancer predisposition genes in the fallopian tube. This repository served as the largest set of putative precursor lesions ever published. A database of BRCA mutation carrier and control group gene expression signatures was established and is currently utilized by breast and ovarian cancer researchers around the world through the Toronto Ovarian Cancer Research Network.	• OCRP Abstract • Tone A, Begley H, Sharma M, et al. 2008. Gene expression profiles of luteal phase fallopian tube epithelium from BRCA mutation carriers resemble high grade serous carcinoma. Clin Cancer Res 14(13):4067-4078. • Vicus D, Shaw P, Finch A, et al. 2010. Risk factors for non-invasive lesions of the fallopian tube in BRCA mutation carriers. Gynecol Oncol 118(3):295-298.
2007	Ovarian Cancer Mutation Frequency and Treatment (Treatment)	Several years after establishing the AOCS database, Dr. Gillian Mitchell and Dr. David Bowtell combined resources under an OCRP Translational Research Partnership Award to sample over 1,000 women with ovarian cancer and found nearly half of women with invasive non-mucinous ovarian cancer and mutations in BRCA1 and BRCA2 did not have a family history. After discovering that women with BRCA1/2 mutations had improved responses to platinum-based chemotherapy at front-line and relapse treatments, in July 2013, Australia revised the genetic testing guidelines to include all women diagnosed with non-mucinous ovarian cancer under the age of 70.	• OCRP Abstract • OCRP Research Highlight • Press Release • Alsop K, Fereday S, Meldrum C, et al. 2012. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: A report from the Australian Ovarian Cancer Study Group. J Clin Oncol 30(21):2654-2663. (http://www.ncbi.nlm.nih.gov/pubmed/?term=22711857)
2008	Platinum Agent Resistance	**MILESTONE FROM THE FIELD:** Platinum agent resistance is found to be the result of reversion of the BRCA2 mutation.	• Sakai W, Swisher E, Karian B, et al. 2008. Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers. Nature 451(7182):1116-1120.
2008	BRCA2 Protein Purified (Risk)	For the first time, under individual BCRP Idea Awards, two teams of scientists at the University of California, Davis successfully purified the full-length protein produced by the BRCA2 gene. Dr. Stephen Kowalczykowski purified the protein from human cells while Dr. Wolf Heyer used genetic engineering techniques to manufacture the human protein in yeast. These complementary approaches enabled the researchers to confirm the role of BRCA2 in repairing damaged DNA. In October 2010, two landmark papers were published describing Dr. Kowalczykowski and Dr. Heyer's respective techniques and complementary conclusions.	• BCRP Abstract – Dr. Stephen Kowalczykowski • BCRP Abstract – Dr. Wolf Heyer • BCRP Research Highlight • Liu J, Doty T, Gibson B, et al. 2010. Human BRCA2 protein promotes RAD51 filament formation on RPA-covered single-stranded DNA. Nat Struct Mol Biol 17(10):1260-1262. • Jensen R, Carreira A, and Kowalczykowski S. 2010. Purified human BRCA2 stimulates RAD51-mediated recombination. Nature 467(7316):678-683.

Year	Title	BRCA Milestones and DoD BCRP/OCRP Research Contributions	Additional Information and Hyperlinks
2009	Olaparib Phase II Trial	**MILESTONE FROM THE FIELD:** Phase II trial of the oral PARP inhibitor olaparib in BRCA-deficient advanced cancer. Two years later, 400 mg twice per day olaparib as a monotherapy is found to be an appropriate dose for future clinical studies in patients with BRCA-mutated cancers.	• Gelmon K, Tischkowitz M, Mackay H, et al. 2011. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: A phase 2, multicentre, open-label, non-randomised study. Lancet Oncol 12:852-861. • Phase II Study of AZD2281 in Patients With Known BRCA Mutation Status or Recurrent High Grade Ovarian Cancer or Patients With Known BRCA Mutation Status/Triple Negative Breast Cancer.
2009	Genetic Loci and Ovarian Cancer Risk (Risk)	Using funds from an OCRP Idea Development Award, Dr. Fergus Couch at the Mayo Clinic identified a genetic locus associated with risk of ovarian cancer in BRCA1 mutation carriers, but not in BRCA2 mutation carriers or the general population. This was the first published report for a BRCA1-specific risk for ovarian cancer.	• OCRP Abstract • OCRP Research Highlight • Couch F, Wang X, McGuffog L, et al. 2013. Genome-wide association study in BRCA1 mutation carriers identifies novel loci associated with breast and ovarian cancer risk. PLoS Genet 9(3):e1003212.
2009	Drug Sensitivity Correlated with BRCA1 (Treatment)	Supported by a BCRP Postdoctoral Fellowship Award and under the mentorship of Dr. Bing Xia, Rachel Anantha from Rutgers University shed light on the role of BRCA1 and Heterogeneous Nuclear Ribonucleoprotein C (hnRNP C) in recombination repair. hnRNP C is one of the most abundant proteins in the nucleus and is a core component of 40S ribonucleoprotein particles that bind pre-mRNAs and influence their processing, stability, and export. Using tandem affinity purification, Dr. Anantha further identified hnRNP C as a component of a nucleoprotein complex containing breast cancer suppressor proteins PALB2, BRCA2, and BRCA1. Results from localization, gene silencing, and quantitative reverse transcriptase PCR established hnRNP C as a key regulator of BRCA gene expression and homologous recombination (HR) based DNA repair. The results also suggested the existence of an RNA regulatory program at sites of DNA damage, which involves a unique function of hnRNP C. Studies are underway to determine if mutations that abrogate homologous recombination activity can be targeted for therapy.	• BCRP Abstract • Anantha R, Alcivar A, Ma J, et al. 2013. Requirements of heterogeneous nuclear ribonucleoprotein C for BRCA gene expression and homologous recombination. PLoS One 8(4):e1368.
2010	National HBOC Week	**MILESTONE FROM THE FIELD:** Breast cancer advocates are successful in their effort to pass a congressional resolution declaring the first-ever National Hereditary Breast and Ovarian Cancer (HBOC) Week and National Previvor Day. HBOC Week marks the transition between Ovarian Cancer Awareness Month in September and Breast Cancer Awareness Month in October.	• http://www.facingourrisk.org

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2010	Preventive Surgery Deemed Effective	**MILESTONE FROM THE FIELD:** Preventative surgery confirmed to reduce breast and ovarian cancer risk in women with BRCA mutations.	• Domcheck S, Friebel T, Sincer C, et al. 2010. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA 304(9):967-975.
2011	Results of Large Familial BRCA Study	**MILESTONE FROM THE FIELD:** In the largest study of its kind, Stanford University School of Medicine researchers found that female first-degree relatives of patients with breast cancer caused by BRCA1 or BRCA2 mutations – but who do not have the mutation themselves – have no higher risk of breast cancer than relatives of patients with other types of breast cancer. The multinational, population-based study involving more than 3,000 families addressed the question of whether a familial BRCA mutation in and of itself was a risk factor, regardless of one being a carrier or noncarrier.	• Kurian A, Gong G, et al. 2011. Breast cancer risk for noncarriers of family-specific BRCA1 and BRCA2 mutations: Findings from the Breast Cancer Family Registry. J Clin Oncol 29(34):4505-4509.
2012	First BRCA-Focused Research Center Opens	**MILESTONE FROM THE FIELD:** The first comprehensive BRCA-focused research center opens. The Basser Research Center focuses exclusively on BRCA1 and BRCA2 with research initiatives ranging from the basic biology of BRCA-related cancers to communication of BRCA test results within families.	• Basser Research Center
2014	Know:BRCA Online Tool	**MILESTONE FROM THE FIELD:** The Centers for Disease Control and Prevention and Bright Pink launch Know:BRCA, an online tool for individuals to learn about BRCA gene mutations and assess their own possible risk of having a BRCA mutation. The Know:BRCA tool is also available for clinicians. Together, these tools are intended to help individuals make important health decisions together with their physicians.	• Know:BRCA Online Tool